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09/687,051	10/12/2000	Kenneth F. Buechler	030691.0008.CON1	6959

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EXAMINER
GABEL, GAILENE

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 11/06/2002 12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/687,051	BUECHLER ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-74 and 79-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-74 and 79-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's amendment and response filed 1/7/02 in Paper No. 10 is acknowledged and has been entered. Claims 55-68 and 75-78 have been cancelled. Claims 79-93 have been added. Accordingly, claims 69-74 and 79-93 are pending and are under examination.

Rejections Withdrawn

Claim Rejections - 35 USC § 112/102/103

2. In light of Applicant's arguments, the rejection of claims 69-74 under 35 U.S.C. 112, second paragraph, is hereby, withdrawn.

3. In light of Applicant's arguments, the rejection of claims 69-72 and 74 under 35 U.S.C. 102(b) as being anticipated by Bodor et al. (Clinical Chemistry, 1992), is hereby, withdrawn.

4. In light of Applicant's arguments, the rejection of claim 73 under 35 U.S.C. 103(a) as being unpatentable over Bodor et al. (Clinical Chemistry, 1992) is hereby, withdrawn.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 69-74 and 79-93 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a cocktail of antibodies, each having specific binding for one of the free cTnI, binary complex of cTnI, and ternary complex of cTnI for use in an assay for determining free and complexed cardiac specific isoforms of troponin (cTnI), does not reasonably provide enablement for a single antibody, having specific binding for each and all of free cTnI, binary complex of cTnI, and ternary complex of cTnI for use in an assay for determining free and complexed cTnI. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As set forth in In re Wands, 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The nature of the invention- the invention is directed to a cocktail of antibodies having specific binding for each one of the free, binary complex, and ternary complex

isoforms of cTnI for use in a method for determining the presence or amount of all free and complexed isoforms of cTnI.

The state of the prior art- the prior art of record fails to disclose an antibody having specific binding for each and all of the free, binary, and ternary complexed isoforms of cTnI for use in a method for determining the presence or amount of all free, binary and ternary complexed isoforms of cTnI.

The predictability or lack thereof in the art- there is no predictability based on the instant specification that a single antibody has specific binding for each and all of the free, binary, and ternary complexed isoforms of cTnI for use in a method of determining the presence or amount of all of the free, binary and ternary complexed isoforms of cTnI in a sample.

The amount of direction or guidance present- appropriate guidance is provided by the specification for a cocktail of antibodies that have been generated to specifically bind each one of the free, binary, and ternary complexed isoforms of cTnI for use in a method to determine the presence or amount of all of the free, binary and ternary complexed isoforms of cTnI in a sample. However, the specification fails to provide any guidance to provide a single antibody that specifically binds all of the free, binary and ternary complexed isoforms of cTnI to determine the total concentration of a cTnI isoform the claimed in an assay.

The presence or absence of working examples- working examples are provided in the specification that show a cocktail of antibodies that specifically bind each one of the free, binary, and ternary complexed isoforms of cTnI for use in determining all of the

free, binary and ternary complexed isoforms of cTnI in a sample. There are no working examples that show analogous results using a single antibody, which is encompassed by the broad scope of the instant claims.

The quantity of experimentation necessary- it would require undue amount of experimentation for the skilled artisan to make and use the method as claimed.

The relative skill of those in the art-the level of skill in the art is high.

The breadth of the claims- as recited, the instant claims are directed to a single antibody that specifically binds all of the free, binary and ternary complexed isoforms of cTnI for use in a method of determining the presence or amount of all free, binary, and ternary complexed isoforms of cTnI in a sample. As recited, the instant single antibody has specific binding for each of the free, binary, and ternary complexed isoforms of cTnI and is capable of determining the presence or amount of all of free, binary, and ternary complexed isoforms of cTnI in as sample.

In this case, the specification at pages 6-7 describes antibodies for use in the claimed method that are monoclonal, polyclonal, fragment thereof, and recombinant . These antibodies are characterized as being "sensitive" or "insensitive", the sensitive antibodies tend to bind and exhibit preferential detection of a single form of troponin and the insensitive antibodies tend to bind and exhibit detection of more than one form of troponin. In pages 13-14, the specification shows that an insensitive antibody is utilized to bind to the free and complexed forms of troponin; that is, insensitive with respect to the oxidized, reduced, and complexed forms of troponin. Alternatively, more than one sensitive antibody would be necessary to measure both the free and complexed forms

of troponin. At pages 21-22, the specification shows how to generate and select antibodies that are sensitive or insensitive to the binding of free troponin I or T, troponin I or T in binary complexes, and troponin I or T in ternary I/T/C complexes; this is accomplished by purification of free troponin I or T, binary troponin I/T, T/C, and I/C complexes and ternary I/T/C complexes, respectively, then injection into mice or rabbits to generate monoclonal or polyclonal antibodies. The antibodies are then screened for affinity and specificity with the purified free troponin, binary complexes of troponin, and ternary complexes of troponin.

While the specification at pages 29-31 exemplifies a selected antibodies, i.e. a cocktail of antibodies, that bind one of the free cTnI, binary complexed cTnI, and ternary complexed cTnI, for use in the claimed method of determining the amount of free, binary complexed, and ternary complexed cTn, the specification does not show any working examples of a single antibody that has specific binding for all of the free cTn, binary complexed cTn, and ternary complexed cTn. The fact that insensitive antibodies that bind more than one form of cTnI has been characterized, is not sufficient to enable the breadth of the claimed method to use a single insensitive antibody in an assay to determine the presence or amount of all of free cTn, binary complexed cTn, and ternary complexed cTn. The specification does not establish a direct correlation between using a cocktail of insensitive and/or sensitive antibodies and a single "insensitive" antibody, which would lead the skilled artisan to say that the claimed method works for a single insensitive antibody to enable the breadth of the claimed method. The specification does not provide any teaching that suggests that an antibody generated against purified

free cTnI, an antibody generated against purified binary complexed cTnI, or an antibody generated against purified ternary complexed cTnI, can be characterized to bind a conserved epitope for each and all of said free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample. Further, the working examples at Example 15 and Example 16, also utilize a cocktail of antibodies to determine the presence or amount of all of free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample. While it is not necessary to show working examples for every possible embodiment, there should be sufficient teachings in the specification that would suggest to the skilled artisan that the breadth of the claimed method is enabled. This is not the case in the instant specification. Thus, the claimed method is only enabled for a cocktail of antibodies having binding specificity for each one of the free cTnI, binary complexed cTnI, and ternary complexed cTnI for use in a method of determining the presence of all of free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample.

In view of the teachings of In re Wands, 8 USPQ2d 1400, it has been determined that the level of experimentation required to enable the breadth of the claims is undue. It has been set forth above that 1) the experimentation required to enable a single antibody to determine the presence of all of free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample, would be great as 2) there is no experimental evidence provided that would indicate that the claimed method would work using a single insensitive antibody; 3) there is no proper guidance that shows that a single insensitive antibody has been generated, characterized, and selected to bind each and all of free cTn, binary complexed cTn and ternary complexed cTn, 4) the nature of the

invention is a cocktail of antibodies having binding specificity for each one of the free cTnI, binary complexed cTnI, and ternary complexed cTnI for use in a method of determining the presence of all of free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample, 5) the relative skill of those in the art is high, yet 6) the state of the prior art has been shown to be unpredictable as evidenced by the fact that no prior art has been cited that shows generation, characterization, and selection of an antibody that has specific binding for each and all of free cTn, binary complexed cTn, and ternary complexed cTn , and lastly 7) the claims broadly recite a single antibody having binding specificity for each of free cTnI, binary complexed cTnI, and ternary complexed cTnI for use in a method of determining the presence of all of free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample, without specifically stating how this can be done without undue experimentation.

Therefore, it is maintained that one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

As stated in the specification at page 11, lines 21-22 "an insensitive antibody which is useful in an immunoassay does not distinguish one form or forms of troponin

from another", in this case, cardiac troponin I, from here on cTnI forms". Further stated at page 6, lines 16-17, "an insensitive antibody is one that will tend to bind more than one form of troponin", in this case cTnI forms, i.e. free cTnI and complexed cTnI". Alternatively, a "sensitive antibody distinguishes one form or forms of cTnI from another form". By those definitions, Examiner interprets the claimed "insensitive antibody" as antibody that specifically binds cTnI, wherein the antibody does not differentially bind, or otherwise has reactivity towards all the recited cTnI forms including 1) free cTnI; 2) cTnI in a binary complex with troponin C (TnC), from here on cTnI/TnC complex; and 3) cTnI in a ternary complex with troponin T (TnT), from here on TnI/TnC/TnT complex; or wherein the antibody has equal affinity to all three forms of cTnI recited.

Claims 79-93 are drawn to a composition comprising *one or more* antibodies or fragments thereof, wherein *each form of cTnI* selected from the group consisting of *free cTnI, cTnI/TnC complex, and cTnI/TnC/TnT* complex *binds one or more* of said antibodies. Accordingly,

6. Claims 79-93 are rejected under 35 U.S.C. 102(b) as being anticipated by Bodor et al. (Clinical Chemistry, 1992).

Bodor et al. develop monoclonal antibodies that bind human cTnI for use in troponin immunoassays. Bodor et al. specifically use purified cTnI in assessing characterization of the monoclonal antibodies (see Abstract page 2204). The cardiac specificity of the purified mAbs was assessed using solid phase ELISA wherein each antibody was tested to observe for binding with cTnI (cTnI coated plates) and cTnI /TnC complex (TnC/TnI-coated plates). In mAb competitive studies using microplates coated

with cTnI/TnC complex, Bodor et al. disclose that some mAbs are insensitive, i.e. bind and recognize different epitopes of cTnI, such as mAbs 3C5.10 and 1E11.3 which have reactivity towards free cTnI and enhanced reactivity towards cTnI/TnC complexes. Bodor et al. further found that 5 other mAbs, including mAbs 2B1.9, 7B11.4, 3D11.11, 1D12.6, and 2F6.6, are also insensitive with respect to each of the cTnI and cTnI/TnC forms, i.e. have reactivity to cTnI and cTnI/TnC complexes or independently bind both free and complexed cTnI (react with cTnI regardless of the presence of TnC). Bodor et al. also identify some mAbs as sensitive, i.e. specifically bind and recognize the same epitopes of cTnI, i.e. 5D4.1 mAb which binds and recognizes only specifically cTnI/TnC complexes (see page 2205 and 2207 column 2, Figure 1). In page 2206, column 1, Bodor et al. disclose the insensitive mAbs as being immobilized on a solid phase (microtiter plates) and the mAbs as being conjugated to a signal generating element (alkaline phosphatase labeled) in order to assess their suitability for use in assays (see page 2206, column 1). Finally, Bodor et al. teach that in ELISA of cTnI, use of mAbs allows greater reproducibility of reagents than polyclonal antibodies (see page 2212, column 2).

Response to Arguments

7. Applicant's arguments with respect to claims 69-74 have been considered but are moot in view of the new grounds of rejection.

8. For reasons aforementioned, no claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday, 6:30 AM - 4:00 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 308-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel
Patent Examiner
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11/13/02

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11/04/02